

Ramucirumab as Second-Line Treatment in Patients With Advanced Hepatocellular Carcinoma

Analysis of REACH Trial Results by Child-Pugh Score

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 Supplemental content

IMPORTANCE REACH is the first phase 3 trial to provide information on hepatocellular cancer (HCC) in the second-line (postsorafenib) setting categorized by Child-Pugh score, a scoring system used to measure the severity of chronic liver disease. This exploratory analysis demonstrates the relationship between a potential ramucirumab survival benefit, severity of liver disease, and baseline α -fetoprotein (α FP).

OBJECTIVE To assess treatment effects and tolerability of ramucirumab by Child-Pugh score in patients with HCC enrolled in the REACH trial.

DESIGN, SETTINGS, AND PARTICIPANTS Randomized, double-blind, phase 3 trial of ramucirumab and best supportive care vs placebo and best supportive care as second-line treatment in patients with HCC enrolled between November 4, 2010 and April 18, 2013, from 154 global sites. Overall, 643 patients were randomized and included in this analysis; 565 patients considered Child-Pugh class A (Child-Pugh scores 5 and 6) and 78 patients considered class B (Child-Pugh scores 7 and 8).

INTERVENTIONS Ramucirumab (8 mg/kg) or placebo intravenously plus best supportive care every 2 weeks.

MAIN OUTCOMES AND MEASURES Overall survival (OS), defined as time from randomization to death from any cause.

RESULTS In the randomized population of 643 patients (mean [SD] age, 62.8 [11.1] years) in this analysis, a potential ramucirumab OS benefit was observed for patients with a Child-Pugh score of 5 (hazard ratio [HR], 0.80; 95% CI, 0.63-1.02; $P = .06$) but no apparent benefit for patients with Child-Pugh scores of 6 or 7 and 8. In patients with baseline α FP levels of 400 ng/mL (to convert ng/mL to μ g/L, multiply by 1.0) or more, a ramucirumab OS benefit was significant for a score of Child-Pugh 5 (HR, 0.61; 95% CI, 0.43-0.87; $P = .01$) and Child-Pugh 6 (HR, 0.64; 95% CI, 0.42-0.98; $P = .04$), but was not significant for Child-Pugh 7 and 8. The overall safety profile of ramucirumab, regardless of Child-Pugh score, was considered manageable. Regardless of treatment arm, patients with Child-Pugh scores of 7 and 8 experienced a higher incidence of grade 3 or higher treatment-emergent adverse events, including ascites and asthenia, and special-interest events, including liver injury and/or failure and bleeding, compared with patients with Child-Pugh scores of 5 or 6.

CONCLUSIONS AND RELEVANCE In unselected patients, a trend for ramucirumab survival benefit was observed only for patients with a Child-Pugh score of 5. In patients with baseline α FP levels of 400 ng/mL or more, a ramucirumab survival benefit was observed for Child-Pugh scores of 5 and 6. Ramucirumab had a manageable toxic effect profile. These results support the ongoing REACH-2 study of ramucirumab in patients with advanced HCC with underlying Child-Pugh A cirrhosis and baseline α FP levels of 400 ng/mL or more.

TRIAL REGISTRATION clinicaltrials.gov Identifier: [NCT01140347](https://clinicaltrials.gov/ct2/show/study/NCT01140347)

JAMA Oncol. 2017;3(2):235-243. doi:[10.1001/jamaoncol.2016.4115](https://doi.org/10.1001/jamaoncol.2016.4115)
Published online September 22, 2016.

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Liver cancer is the sixth most diagnosed cancer worldwide and the second most common cause of cancer death,¹ and hepatocellular carcinoma (HCC) represents the majority of primary liver cancers. In major clinical trials²⁻¹¹ of patients with advanced or unresectable HCC, targeting of the vascular endothelial growth factor (VEGF) pathway with small molecule agents²⁻⁷ or biologic agents⁸⁻¹¹ has been studied. Sorafenib, which targets the VEGF pathway, remains the only approved systemic treatment of HCC, validating the pathway as an important target.^{2,3} Despite 1 recent trial¹² of the multitargeted kinase inhibitor regorafenib reporting a significantly improved overall survival (OS) in the second-line setting, multiple other trials have been unable to demonstrate a survival benefit in both first-line and second-line settings and additional treatment options for HCC continue to be a highly unmet need.^{4-7,11,13-15}

The REACH trial¹¹ evaluated the safety and efficacy of the anti-VEGFR-2 monoclonal antibody ramucirumab in patients with advanced HCC who had received first-line sorafenib. In the intention-to-treat (ITT) Child-Pugh class A population, the OS for patients who received second-line ramucirumab was not significantly longer than for patients who received placebo. However, in the prespecified subgroup of patients with baseline α -fetoprotein (α FP) levels 400 ng/mL (to convert ng/mL to μ g/L, multiply by 1.0) or more, patients who received ramucirumab did achieve significantly longer OS compared with those who received placebo (hazard ratio [HR], 0.67; 95% CI, 0.51-0.90; $P = .01$).

Chronic liver disease is often present in patients with HCC and complicates HCC treatment. The Child-Pugh score is frequently used to select or stratify patients in HCC trials.¹⁶⁻¹⁹ The score uses 5 clinical and laboratory measures (total bilirubin, serum albumin, prothrombin ratio, ascites, and hepatic encephalopathy) to generate a total score between 5 and 15. Patients with scores of 5 or 6 have Child-Pugh class A disease and are considered to have a relatively good prognosis regarding chronic liver disease; patients with scores of 7, 8, or 9 have Child-Pugh class B disease and have an intermediate prognosis; and patients with scores 10 or greater have Child-Pugh Class C disease and have considerably worse survival outcomes.

In general, patients with HCC with Child-Pugh class A liver disease are considered ideal candidates for anticancer therapy. However, patients with Child-Pugh class B or C liver disease are generally excluded from most HCC trials because the severity of underlying liver dysfunction poses challenges to anticancer treatment. Consequently, it is unclear how best to identify patients with Child-Pugh class B or C liver disease who may benefit from an anticancer therapy. Furthermore, most of the data regarding the usefulness of the Child-Pugh score in HCC have come from early in the disease course or in first-line systemic treatment; to our knowledge, no data on any relationship between Child-Pugh score and treatment outcomes are available in prospective trials in the second-line setting.

We performed the current exploratory analysis to assess the treatment effect and tolerability of ramucirumab by Child-Pugh score in patients with HCC enrolled in the REACH study.

Key Points

Question Is there a survival benefit for ramucirumab in the second-line setting for patients with hepatocellular carcinoma (HCC) when examined by Child-Pugh score and baseline α -fetoprotein (α FP) levels?

Findings In unselected patients, a trend for ramucirumab survival benefit was observed in patients with HCC in the Child-Pugh 5 disease subgroup. For patients with baseline α FP levels 400 ng/mL or more, a significant survival benefit for patients treated with ramucirumab was observed in those with Child-Pugh scores of 5 and 6.

Meaning A potential survival benefit in patients with HCC treated with ramucirumab was observed in patients with baseline α FP levels of 400 ng/mL or more. Studies evaluating the predictive value of α FP levels in patients with HCC treated with ramucirumab are warranted.

The population of all randomized patients by Child-Pugh score and the population based on baseline α FP levels and Child-Pugh score were evaluated.

Methods

Patient Population

REACH¹¹ was a randomized, double-blind, placebo-controlled phase 3 trial with enrollment in 154 global sites; patients with HCC Child-Pugh class A and class B liver disease were randomized ($N = 644$). In the original protocol, patients with Child-Pugh B disease were eligible, and the study was also stratified by Child-Pugh class; based on the independent data monitoring committee evaluation, the protocol was amended to exclude patients with Child-Pugh B disease from future enrollment. The final ITT population comprised only patients with Child-Pugh Class A disease ($n = 565$). For the subgroup of patients with baseline α FP levels 400 ng/mL or more, OS, progression-free survival (PFS), and treatment interaction tests were prespecified. Randomization for the ITT population was stratified by geographic region and etiology of liver disease. Trial methods have been described previously.¹¹ In the current exploratory analysis, patients randomized to REACH were assigned to 3 subgroups based on baseline Child-Pugh score determined from patient case report forms: Child-Pugh 5, Child-Pugh 6, and Child-Pugh 7 and 8 scores. Because of limited patient numbers, patients with a Child-Pugh score of 7 or 8 were combined into a single subgroup to allow meaningful interpretation of the results. The centers' review committees approved the study and all patients provided written informed consent.

Treatment

Patients received either ramucirumab 8 mg/kg (Eli Lilly and Company) or placebo intravenously every 2 weeks until disease progression, unacceptable toxic effects, or withdrawal of consent. All patients received best supportive care.¹¹

Table 1. Baseline Disease Characteristics by Treatment and Child-Pugh Score for All Randomized Patients

Disease Characteristic	Patients, No. (%)					
	Ramucirumab			Placebo		
	CP 5 (n = 177)	CP 6 (n = 108)	CP 7 and 8 (n = 39)	CP 5 (n = 180)	CP 6 (n = 100)	CP 7 and 8 (n = 39)
Baseline BCLC score, stage C	155 (87.6)	98 (90.7)	36 (92.3)	161 (89.4)	85 (85.0)	36 (92.3)
Primary tumor present	155 (87.6)	104 (96.3)	39 (100.0)	156 (86.7)	94 (94.0)	39 (100.0)
Metastatic sites, No.						
0-2	157 (88.7)	98 (90.7)	34 (87.2)	163 (90.6)	89 (89.0)	31 (79.5)
≥3	20 (11.3)	10 (9.3)	5 (12.8)	17 (9.4)	11 (11.0)	8 (20.5)
Etiology of liver disease						
Hepatitis B	81 (45.8)	31 (28.7)	15 (38.5)	75 (41.7)	33 (33.0)	15 (38.5)
Hepatitis C	43 (24.3)	40 (37.0)	12 (30.8)	42 (23.3)	33 (33.0)	12 (30.8)
Significant alcohol use	30 (16.9)	29 (26.9)	12 (30.8)	34 (18.9)	27 (27.0)	10 (25.6)
Steatohepatitis (NASH, fatty liver)	14 (7.9)	6 (5.6)	0 (0.0)	10 (5.6)	9 (9.0)	4 (10.3)
Macrovascular invasion present	43 (24.3)	42 (38.9)	13 (33.3)	45 (25.0)	34 (34.0)	16 (41.0)
Extrahepatic spread present	134 (75.7)	75 (69.4)	29 (74.4)	134 (74.4)	65 (65.0)	26 (66.7)
Age ≥65 y	83 (46.9)	50 (46.3)	21 (53.8)	79 (43.9)	42 (42.0)	15 (38.5)
ECOG PS 0	112 (63.3)	46 (42.6)	11 (28.2)	107 (59.4)	47 (47.0)	15 (38.5)
Reason for discontinuation of sorafenib						
Progressive disease	156 (88.1)	92 (85.2)	32 (82.1)	154 (85.6)	85 (85.0)	34 (87.2)
Toxic effects	21 (11.9)	16 (14.8)	7 (17.9)	26 (14.4)	15 (15.0)	5 (12.8)
α-Fetoprotein						
<400 ng/mL	107 (60.5)	54 (50.0)	15 (38.5)	96 (53.3)	52 (52.0)	20 (51.3)
≥400 ng/mL	68 (38.4)	52 (48.1)	23 (59.0)	83 (46.1)	48 (48.0)	16 (41.0)
Missing	2 (1.1)	2 (1.9)	1 (2.6)	1 (0.6)	0	3 (7.7)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh score; ECOG PS, Eastern Cooperative Oncology Group performance status; NASH, nonalcoholic steatohepatitis.

Outcomes

Overall survival was defined as the time from randomization to death from any cause, and PFS was defined as the time from randomization to radiographic progression or death. Tumor response was assessed by protocol-defined criteria based on Response Evaluation Criteria in Solid Tumours 1.1; objective response rate was defined as the proportion of patients who achieved complete response plus partial response as their best overall response; disease control rate was defined as the proportion of patients who achieved complete response plus partial response plus stable disease as their best overall response. Safety data were collected continuously until 30 days after the completion of study treatment.

Statistical Methods

Overall survival, PFS, and tumor response rates were analyzed for each Child-Pugh score subgroup, including both αFP groups (baseline αFP ≥ 400 ng/mL or <400 ng/mL). Analyses were designed to compare treatments within Child-Pugh and αFP groups. Overall survival and PFS were analyzed using the Kaplan-Meier method. An unstratified log-rank test was used to compare treatment effect, and unstratified Cox regression models were used to generate the HRs. Objective response rate and disease control rate were compared between the 2 treatment groups using a Cochran-Mantel-Haenszel test. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

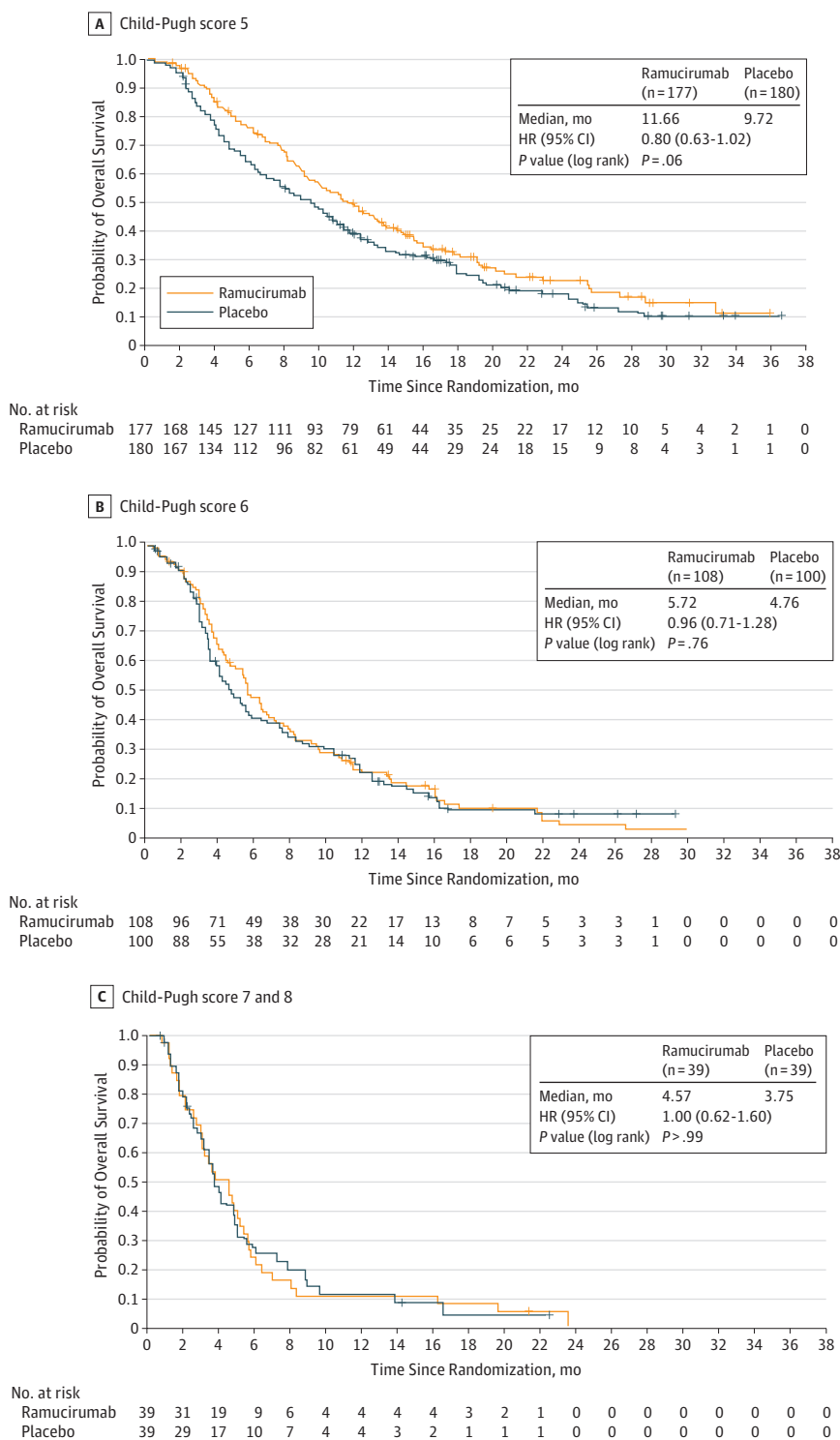
Treatment-emergent adverse event data are presented as frequencies and proportions.

Results

Between November 4, 2010, and April 18, 2013, 644 patients were randomized, of which 357 patients with a baseline Child-Pugh score of 5 (n = 177 ramucirumab; n = 180 placebo), 208 with a baseline Child-Pugh score of 6 (n = 108 ramucirumab; n = 100 placebo), and 78 with a baseline Child-Pugh score of 7 and 8 (n = 39 ramucirumab; n = 39 placebo) were identified. One patient with a baseline Child-Pugh score of 9 was randomized but was not included in this exploratory analysis. Baseline patient and tumor characteristics were generally balanced between treatment groups by Child-Pugh score (Table 1). A lower percentage of patients with a Child-Pugh score of 7 and 8 had a performance status of 0 in relation to the Child-Pugh 5 or 6 populations in both the ramucirumab and placebo arms. Other than performance status, no clear trends were identified in the other baseline characteristics comparing patients with Child-Pugh scores of 5, 6, and Child-Pugh scores of 7 and 8.

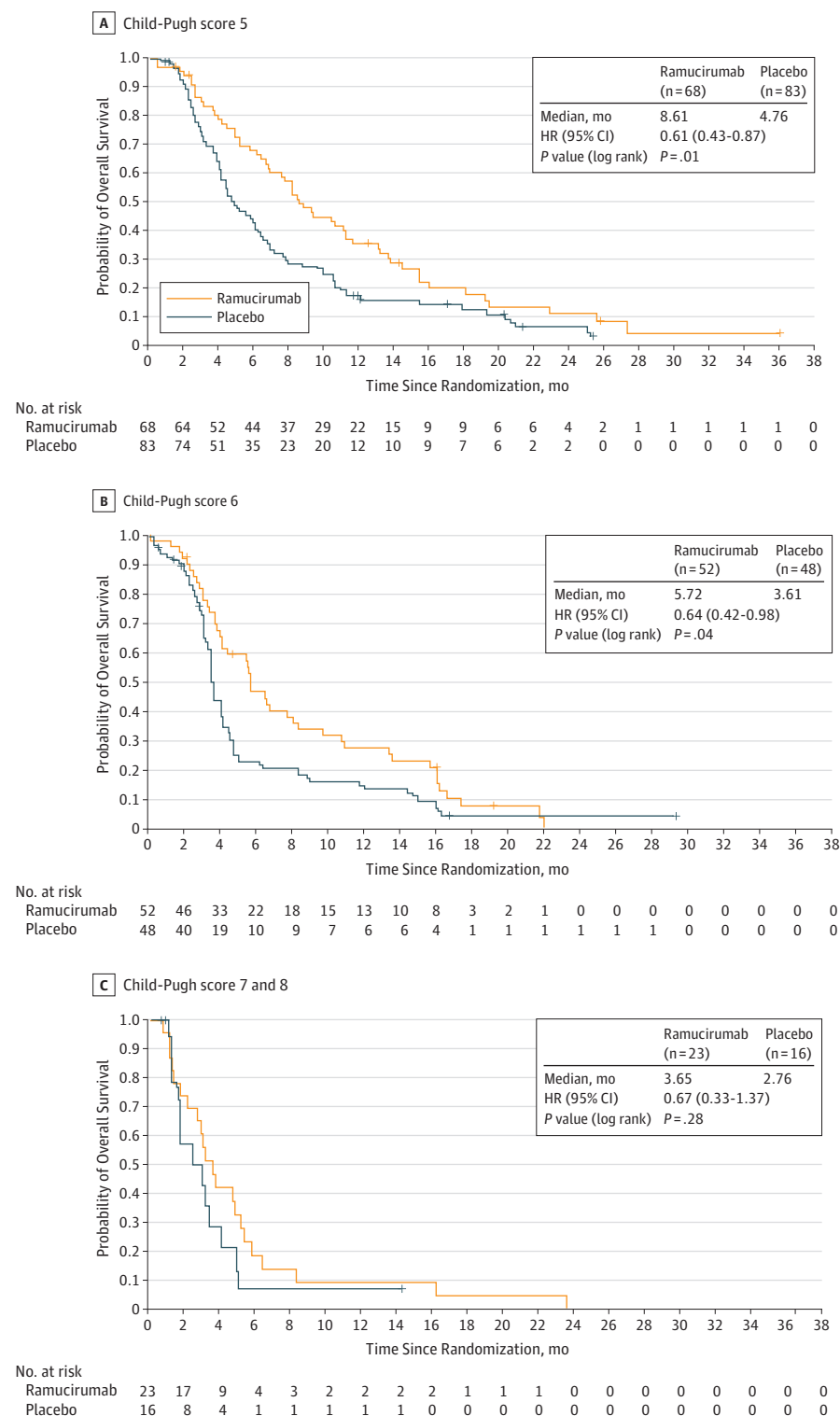
Figure 1 depicts the OS curves of each Child-Pugh score subgroup. In the ITT population, a potential ramucirumab treatment OS benefit was observed for patients with a Child-Pugh score of 5 (HR, 0.80; 95% CI, 0.63-1.02; *P* = .06), but no apparent benefit for patients with Child-Pugh scores of 6 or 7 and 8 (HR, 0.96; 95%

Figure 1. Overall Survival for All Randomized Patients



CI, 0.71-1.28; $P = .76$ and HR, 1.00; 95% CI, 0.62-1.60; $P = >.99$, respectively). The PFS HRs were 0.59 (95% CI, 0.47-0.74; $P < .001$) for patients with a Child-Pugh score of 5; 0.78 (95% CI, 0.58-1.04; $P = .09$) for patients with a Child-Pugh score of 6; and 0.74 (95% CI, 0.46-1.19; $P = .22$) for patients with Child-Pugh scores of 7 and 8 (eFigure 1 in the Supplement).

In patients with baseline α FP levels 400 ng/mL or more ($n = 290$), OS was favorable for Child-Pugh scores of 5 (HR, 0.61; 95% CI, 0.43-0.87; $P = .01$) and Child-Pugh scores of 6 (HR, 0.64; 95% CI, 0.42-0.98; $P = .04$) (Figure 2). The PFS was favorable for patients with a Child-Pugh score of 5 (HR, 0.66; 95% CI, 0.47-0.93; $P = .02$) (eFigure 2 in the Supplement). In

Figure 2. Overall Survival for Patients With Baseline α -Fetoprotein Levels 400 ng/mL or More

patients with baseline α FP levels less than 400 ng/mL ($n = 344$), no apparent OS improvement was observed in any Child-Pugh subgroup, and improvement in PFS was observed in the Child-Pugh 5 subgroup (eFigures 3 and 4 in the Supplement).

Improvement in objective response rate with ramucirumab treatment was observed in patients with Child-Pugh scores of 5 or 6, although this was not significant in the Child-Pugh 6 subgroup (Table 2). Significant improvement of

Table 2. Tumor Response by Child-Pugh Score for All Randomized Patients

Tumor Response	No. (%)								
	Child-Pugh 5			Child-Pugh 6			Child-Pugh 7 and 8		
	Ramucirumab (n = 177)	Placebo (n = 180)	P Value	Ramucirumab (n = 108)	Placebo (n = 100)	P Value	Ramucirumab (n = 39)	Placebo (n = 39)	P Value
Objective response ^a	15 (8.5)	1 (0.6)	<.001	6 (5.6)	1 (1.0)	.09	0	1 (2.6)	.41
Disease control rate ^b	110 (62.1)	83 (46.1)	.001	51 (47.2)	45 (45.0)	.87	19 (48.7)	11 (28.2)	.04
Complete response	1 (0.6)	0	NA	0	0	NA	0	0	NA
Partial response	14 (7.9)	1 (0.6)	NA	6 (5.6)	1 (1.0)	NA	0	1 (2.6)	NA
Stable disease	95 (53.7)	82 (45.6)	NA	45 (41.7)	44 (44.0)	NA	19 (48.7)	10 (25.6)	NA
Progressive disease	57 (32.2)	87 (48.3)	NA	40 (37.0)	43 (43.0)	NA	12 (30.8)	19 (48.7)	NA
Not evaluable	10 (5.6)	10 (5.6)	NA	17 (15.7)	12 (12.0)	NA	8 (20.5)	9 (23.1)	NA

Abbreviation: NA, not applicable.

^a Objective response includes patients who experienced either complete response or partial response.^b Disease control rate includes patients who experienced complete response, partial response, or had stable disease.

Table 3. Treatment-Emergent Adverse Events Reported in Patients in Ramucirumab Arm by Treatment and Child-Pugh Score for the Safety Population

Adverse Event	No. (%)											
	Any Grade ^a						Grade ≥3					
	Ramucirumab			Placebo			Ramucirumab			Placebo		
	CP 5 (n = 173)	CP 6 (n = 106)	CP 7 and 8 (n = 38)	CP 5 (n = 177)	CP 6 (n = 97)	CP 7 and 8 (n = 38)	CP 5 (n = 173)	CP 6 (n = 106)	CP 7 and 8 (n = 38)	CP 5 (n = 177)	CP 6 (n = 97)	CP 7 and 8 (n = 38)
Patients with any TEAE	168 (97.1)	104 (98.1)	38 (100)	165 (93.2)	93 (95.9)	37 (97.4)	102 (59.0)	68 (64.2)	35 (92.1)	73 (41.2)	56 (57.7)	24 (63.2)
Edema peripheral	56 (32.4)	49 (46.2)	13 (34.2)	23 (13.0)	26 (26.8)	7 (18.4)	0	1 (0.9)	0	0	1 (1.0)	0
Fatigue	42 (24.3)	23 (21.7)	9 (23.7)	39 (22.0)	18 (18.6)	5 (13.2)	3 (1.7)	4 (3.8)	2 (5.3)	4 (2.3)	4 (4.1)	0
Headache	39 (22.5)	15 (14.2)	1 (2.6)	10 (5.6)	5 (5.2)	1 (2.6)	2 (1.2)	0	0	0	0	0
Hypertension	39 (22.5)	16 (15.1)	4 (10.5)	14 (7.9)	7 (7.2)	1 (2.6)	28 (16.2)	6 (5.7)	1 (2.6)	6 (3.4)	4 (4.1)	1 (2.6)
Decreased appetite	36 (20.8)	28 (26.4)	15 (39.5)	33 (18.6)	16 (16.5)	5 (13.2)	3 (1.7)	3 (2.8)	2 (5.3)	2 (1.1)	0	0
Nausea	36 (20.8)	18 (17.0)	14 (36.8)	34 (19.2)	18 (18.6)	8 (21.1)	0	0	0	0	0	0
Abdominal pain	32 (18.5)	18 (17.0)	5 (13.2)	39 (22.0)	22 (22.7)	7 (18.4)	5 (2.9)	0	2 (5.3)	5 (2.8)	7 (7.2)	1 (2.6)
Ascites	31 (17.9)	45 (42.5)	10 (26.3)	17 (9.6)	21 (21.6)	10 (26.3)	6 (3.5)	7 (6.6)	6 (15.8)	6 (3.4)	4 (4.1)	7 (18.4)
Diarrhea	31 (17.9)	24 (22.6)	6 (15.8)	25 (14.1)	13 (13.4)	7 (18.4)	1 (0.6)	2 (1.9)	0	1 (0.6)	1 (1.0)	1 (2.6)
Proteinuria	31 (17.9)	14 (13.2)	0	7 (4.0)	6 (6.2)	1 (2.6)	4 (2.3)	2 (1.9)	0	0	0	0
Asthenia	29 (16.8)	20 (18.9)	12 (31.6)	18 (10.2)	17 (17.5)	5 (13.2)	10 (5.8)	4 (3.8)	4 (10.5)	2 (1.1)	3 (3.1)	2 (5.3)
Cough	29 (16.8)	14 (13.2)	4 (10.5)	18 (10.2)	5 (5.2)	6 (15.8)	1 (0.6)	0	0	0	0	0
Thrombocytopenia	28 (16.2)	22 (20.8)	6 (15.8)	8 (4.5)	4 (4.1)	2 (5.3)	8 (4.6)	5 (4.7)	2 (5.3)	0	1 (1.0)	0
Epistaxis	24 (13.9)	15 (14.2)	11 (28.9)	11 (6.2)	6 (6.2)	6 (15.8)	0	0	0	0	0	0
Pyrexia	24 (13.9)	23 (21.7)	7 (18.4)	11 (6.2)	15 (15.5)	7 (18.4)	1 (0.6)	0	0	1 (0.6)	0	0
Constipation	23 (13.3)	15 (14.2)	1 (2.6)	22 (12.4)	12 (12.4)	4 (10.5)	0	0	0	0	0	0
Abdominal pain upper	21 (12.1)	6 (5.7)	4 (10.5)	13 (7.3)	11 (11.3)	6 (15.8)	1 (0.6)	1 (0.9)	0	0	1 (1.0)	0
Vomiting	21 (12.1)	11 (10.4)	9 (23.7)	22 (12.4)	16 (16.5)	4 (10.5)	2 (1.2)	0	0	0	2 (2.1)	0
Pruritus	20 (11.6)	8 (7.5)	7 (18.4)	18 (10.2)	11 (11.3)	5 (13.2)	0	0	0	0	1 (1.0)	0
Rash	18 (10.4)	6 (5.7)	3 (7.9)	5 (2.8)	7 (7.2)	1 (2.6)	0	0	0	0	0	0

Abbreviations: CP, Child-Pugh score; TEAE, treatment-emergent adverse events.

^a Included are any-grade treatment-emergent adverse events that occurred in ≥10% of ramucirumab patients with a Child-Pugh 5 score.

disease control rate was observed in patients with Child-Pugh scores of 5 and scores of 7 and 8.

The most frequent treatment-emergent adverse events (TEAEs) of any grade that were higher on the ramucirumab arm included peripheral edema, headache, and hypertension in the Child-Pugh 5 subgroup (n = 350), and peripheral edema,

ascites, and decreased appetite in the Child-Pugh 6 subgroup (n = 203) (Table 3). The most frequent adverse events of special interest (AESI) of any grade in the Child-Pugh 5 or 6 subgroups that were higher on the ramucirumab arm included liver injury and/or failure, bleeding, and hypertension (eTable in the Supplement). Hypertension was the only grade 3 or higher

TEAE and/or AESI observed in 10% or more of patients in the ramucirumab arm and higher than placebo (>5% difference). Overall, the safety profile of ramucirumab was manageable in the Child-Pugh 5 and 6 subgroups.

For the Child-Pugh 7 and 8 subgroup ($n = 76$), the most frequent TEAEs of any grade that were higher in the ramucirumab arm included decreased appetite, nausea, asthenia, and peripheral edema (Table 3). The most frequent AESIs of any grade that were higher in the ramucirumab arm included liver injury and/or failure, hypertension, and infusion-related reactions (eTable in the Supplement). The incidence of any-grade liver injury and/or failure AESIs, including clinical and laboratory events, was higher in the ramucirumab arm (81.6%) compared with the placebo arm (55.3%). However, when adjusted for duration of exposure to study treatment, there was no difference between treatment arms in the Child-Pugh 7 and 8 subgroup (incidence rates per 100 patient years: 326.1 [ramucirumab] vs 321.5 [placebo]). Hepatic encephalopathy and asthenia in the Child-Pugh 7 and 8 subgroup were the only grade 3 or higher TEAEs and/or AESIs observed in 10% or more of patients in the ramucirumab arm and higher than placebo (>5% difference); the number of patients who experienced encephalopathy was low ($n = 4$), and no grade 5 instances were reported for either event.

In general, regardless of treatment arm, patients with a Child-Pugh score of 7 and 8 appeared to experience a higher incidence of grade 3 or higher TEAEs or AESIs compared with patients with a Child-Pugh 5 or Child-Pugh 6 score. In the Child-Pugh 7 and 8 subgroup compared with Child-Pugh 5 or Child-Pugh 6 subgroups, the only specific grade 3 or higher TEAEs that appeared higher in both treatment arms were ascites and asthenia. Patients with Child-Pugh scores of 7 and 8 also appeared to experience a higher incidence of the grade 3 or higher AESIs of liver injury and/or failure and bleeding and/or hemorrhage compared with patients with a Child-Pugh 5 or Child-Pugh 6 score. Regardless of treatment arm, a higher rate of some adverse events in patients with higher Child-Pugh scores was observed, consistent with adverse events that might be expected in patients with more severe liver dysfunction.²⁰

Overall, the safety profile observed for each Child-Pugh score was consistent with the underlying disease state and with the profile previously demonstrated for single-agent ramucirumab.²¹

Discussion

This analysis of REACH¹¹ provides important insights into the relationship of Child-Pugh score and the efficacy and safety of ramucirumab treatment in patients with advanced HCC. To our knowledge, this is the most comprehensive analysis of the relationship between Child-Pugh score and the results from a phase 3 study in patients undergoing second-line HCC treatment.

Analyses suggest that Child-Pugh class may still be prognostic for survival in the second-line setting. In HCC studies with sorafenib, the prognosis of patients with Child-Pugh class B HCC compared with those with class A HCC is worse,^{20,22,23} although analyses by Child-Pugh score are not commonly reported. In REACH, Child-Pugh scores appeared to be prognos-

tic in patients undergoing second-line HCC treatment, with a shorter survival observed in patients with progressively higher Child-Pugh scores on both treatment arms (Figure 1). It is notable that the median OS in the placebo arm of patients with a Child-Pugh of 6 (4.76 months) was substantially shorter than that of patients with a Child-Pugh score of 5 (9.72 months), as historically the prognosis of patients with Child-Pugh class A liver disease (ie, Child-Pugh 5 and 6 scores) have been considered to be similar.²⁴ However, there are limited data on outcomes as they relate to Child-Pugh score for patients with HCC undergoing second-line treatment after sorafenib, and it is conceivable that differences in the prognosis of Child-Pugh 5 disease and Child-Pugh 6 disease are more prominent in the second-line compared with first-line settings. Whether an alternative to the Child-Pugh score to classify patients' liver function based on objective measures of serum albumin and bilirubin will better characterize prognosis in HCC is still unknown; a recent analyses of the REACH survival results by serum albumin and bilirubin grade defined 3 patient populations with different prognoses.²⁵

In assessing treatment effect, a trend for a ramucirumab survival benefit was only observed in the unselected patient population with a Child-Pugh score of 5; no survival benefit was observed in unselected patient populations with a Child-Pugh score of 6 or 7 and 8. Treatment arm imbalances are unlikely to be the reason for the differential treatment effect by Child-Pugh score because baseline characteristics were generally well balanced in each group. One possibility is that the more severe liver dysfunction, as classified by Child-Pugh score, negatively affects the ability of ramucirumab to produce a survival benefit in patients with advanced HCC. This hypothesis would be consistent with the observed PFS benefit in patients with a Child-Pugh 5 score; survival in patients with higher Child-Pugh scores would be less likely improved by tumor control. Similar to the REACH¹¹ analyses presented here, we also note that recent results of regorafenib as second-line treatment of HCC also appear to favor a better survival in patients with a Child-Pugh score of 5 compared with those with a Child-Pugh 6 score.¹² Confounding of the survival end point by severe liver dysfunction in HCC trials has been proposed by others,²⁶ and our analyses would support this hypothesis.

In selected patients with a baseline α FP level 400 ng/mL or more, an improvement in OS was observed in patients with Child-Pugh class A disease (Figure 2). No OS benefit was observed in any Child-Pugh subgroup with baseline α FP levels less than 400 ng/mL. These results are consistent with the observed survival benefit in the ITT population with baseline α FP levels either 400 ng/mL or more or less than 400 ng/mL reported previously.¹¹ No consistently predictive cancer biomarkers are currently used to guide patient selection for systemic antiangiogenesis treatments. As described previously,¹¹ mounting evidence suggests that in a particular subclass of patients with HCC who have elevated α FP levels and poor prognosis, intratumoral conditions may exist that enhance sensitivity to VEGFR-2 inhibition. Alternatively, there could be other underlying baseline characteristics or posttreatment management factors that contribute to the treatment benefit. We note there was a nonsignificant trend for OS benefit in patients with

Child-Pugh 7 and 8 scores and α FP levels 400 ng/mL or more and that the absolute difference in median OS was modest. However, in unselected patients with Child-Pugh scores of 7 and 8, the disease control rate was significantly higher for ramucirumab. To our knowledge, this is the first report on efficacy for any systemic treatment compared with placebo in patients with Child-Pugh class B liver function. Reasons why PFS and response do not predict survival benefit in patients with baseline α FP levels less than 400 ng/mL, for whom underlying liver disease, cirrhosis, and other unknown factors rather than HCC may lead to death, have been discussed previously.¹¹ Others have also recently reported a poor correlation of PFS and OS in patients with HCC.²⁷

Regardless of Child-Pugh score, the ramucirumab safety profile was generally considered manageable in patients with advanced HCC. In patients with Child-Pugh scores of 5 or 6, hypertension was the only grade 3 or higher TEAE and/or AESI higher in the ramucirumab vs placebo arm (observed in $\geq 10\%$ of patients in the ramucirumab arm and higher than placebo [$>5\%$ difference]). This finding was similar to that with single-agent ramucirumab in the gastric or gastroesophageal junction adenocarcinoma phase III trial (REGARD),²¹ in which 1 of only 2 grade 3 or higher events more common in the ramucirumab arm than in the placebo arm was also hypertension. In patients with Child-Pugh 7 and 8 scores, liver injury, including hepatic encephalopathy, and asthenia were the grade 3 or higher TEAEs or AESIs higher for ramucirumab vs placebo arms (observed in $\geq 10\%$ of patients on the ramucirumab arm and higher than placebo [$>5\%$ difference]). The higher frequency of liver injury and/or failure and bleeding AESIs in the Child-Pugh 7 and 8 subgroup compared with the Child-Pugh 5 or 6 subgroups, regardless of treatment arm, is consistent with other reports of an increased incidence of adverse events related to liver cirrhosis in patients with higher Child-Pugh B scores (Child-Pugh 8 and 9).²⁸ Hence, the differences in the most common TEAEs between the Child-Pugh 5 or 6 and Child-Pugh 7 and 8 subgroups are likely related to the more severe liver dys-

function and cirrhosis in patients with higher Child-Pugh scores. Hepatic encephalopathy is an adverse event that is largely unique to a population with end-stage liver disease, and the patients with Child-Pugh 7 and 8 scores may have been at higher risk for this event compared with patients with lower Child-Pugh scores. A retrospective analysis of prior Child-Pugh class B studies also reported encephalopathy as occurring more frequently in patients with Child-Pugh class B disease compared with patients with Child-Pugh class A disease treated with sorafenib.²⁹ The mechanism for how ramucirumab might increase the risk of hepatic encephalopathy is unknown. Notably, a clear increase in the incidence of many other liver injury and/or failure events was not observed. Currently, ramucirumab is recommended in approved indications (gastric or gastroesophageal junction adenocarcinoma, non-small-cell lung cancer, and colorectal cancer) to be used with caution in patients with Child-Pugh class B (or worse) liver dysfunction.³⁰

Conclusions

This exploratory analysis of REACH¹¹ demonstrates that in unselected patients with a Child-Pugh score of 5, a trend for survival benefit from ramucirumab treatment was observed, but no clear survival benefit was observed in patients with higher Child-Pugh scores. Regardless of Child-Pugh score, a potential ramucirumab survival benefit was observed in patients with a baseline α FP level of 400 ng/mL or more, supporting the use of baseline α FP as a method to identify those patients most likely to benefit from ramucirumab. Ramucirumab had a manageable safety profile regardless of Child-Pugh score. There continues to be high unmet need for an effective treatment for patients with advanced HCC, and further investigation of the efficacy and safety of ramucirumab in patients with HCC and elevated baseline α FP will be evaluated in an ongoing phase 3 trial (REACH-2; [clinicaltrials.gov NCT02435433](http://clinicaltrials.gov/NCT02435433)).

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Accepted for Publication: July 26, 2016.

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Conflict of Interest Disclosures: Dr Zhu reports receiving research support from Eli Lilly and Company. Dr Chau served on advisory boards at Sanofi Oncology, Eli Lilly and Company, Bristol-Myers Squibb, MSD, Merck Serono, and Gilead Sciences; had research funding from Janssen-Cilag, Sanofi Oncology, Roche, Merck

Serono, and Novartis; and received honorarium from Taiho, Pfizer, Amgen, Eli Lilly and Company, and Bayer. Dr Weissinger served on the advisory board for Eli Lilly and Company. Drs Chang, Abada, and Yang are stockholders and employees of Eli Lilly and Company. Dr Okusaka reports honoraria from Chugai Pharmaceutical, Pfizer Japan, Novartis Pharma K.K., Taiho, Merck Serono, Eli Lilly Japan K.K., Sumitomo Dainippon Pharma, Eisai, Bayer Yakuhin, Yakult Honsha, Nobelpharma, Nippon Kayaku, Baxter, and Astellas Pharma; a consulting role at Eli Lilly Japan K.K., Sumitomo Dainippon Pharma, Taiho, Ono Pharmaceutical, Nippon Boehringer Ingelheim, NanoCarrier, and Zeria Pharmaceutical; and research funding from Chugai Pharmaceutical, Eli Lilly Japan K.K., Eisai, Novartis Pharma K.K., Shizuoka Industry, Takeda Bio Development Center Limited, Yakult Honsha, OncoTherapy Science, Otsuka Pharmaceutical, Taiho, Sceti Medical Labo K.K., Nippon Boehringer Ingelheim, Kowa Company, Kyowa Hakko Kirin, Merck Serono, Ono Pharmaceutical, Bayer Yakuhin, Pfizer Japan, AstraZeneca K.K., Sumitomo Dainippon Pharma, Nobelpharma, Zeria Pharmaceutical, and GlaxoSmithKline K.K. No other conflicts are reported.

Funding/Support: This research was supported by Eli Lilly and Company.

Role of the Funder/Sponsor: Eli Lilly and Company contracted with inVentiv Health Clinical for writing support, provided by Emily Cullinan, PhD, and Michelle Mynderse, PhD, and editorial support provided by Noelle Gasco.

Additional Contributions: We thank the patients and their families and/or caregivers, the study investigators and their staff, the independent data monitoring committee, and the REACH clinical trial team.

Published Online: September 22, 2016.
doi:10.1001/jamaoncol.2016.4115

Open Access: This article is published under JAMA Oncology's open access model and is free to read on the day of publication.

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